REMARKS

Entry of the foregoing amendments, reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, Claims 1 through 10 are cancelled in favor of new Claims 11 through 15. These amendments are made in order to expedite prosecution.

Applicants respectfully note that the claims find explicit support at pages 15 and 16, which teach that the optimal effective dosage of the subject chimeric anti-CD20 antibody, and that this dosage results in nearly total peripheral blood B-cell depletion within about 24 hours post-infusion. Support for the additional administration of a chemotherapeutic agent finds support at page 61, with the particular chemotherapeutic agents finding support in the paragraph bridging pages 61 and 62.

Also, Applicants respectfully advise that the above-identified portions of the disclosure are taken verbatim from U.S. Serial No. 08/149,099, filed on November 3, 19993, now U.S. Patent 5,736,137. Specifically, this patent provides explicit support for the claims presented herein at column 8, lines 16-65, and at columns 30 through 32 (combination therapy).

Turning to the Office Action, the objection to the Oath is noted. A new Oath will be provided upon indication of allowance.

The objection to the earlier applications is noted. The specification has been amendment to correct "07/9077,691" to --07/977,691--.

The objection to the Abstract is obviated by the new Abstract provided herewith.

Claims 3 and 8 through 10 were rejected under 35 U.S.C. §112, first paragraph, as being non-enabled. This rejection is respectfully traversed.

Applicants respectfully advise that the transfectoma TCAE8 has been deposited with the American Type Culture Collection on November 4, 1992, 12301 Parklawn Drive, Rockville MD 20852 according to the provisions of the Budapest Treaty. All restrictions on the availability of this cell line were irrevocably removed upon granting of U.S. Patent 5,736,137.

Also, the specification has been amended to include the date of deposit. Previously included were the depository, address, and accession number. Withdrawal of the §112 enablement rejection is respectfully requested.

Claims 3 and 8 through 10 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is moot based on the cancellation of these claims.

The Examiner's comments regarding the alleged lack of priority for the prior claims in U.S. Serial No. 08/149,099 are noted. However, the Examiner's objection is respectfully submitted to be totally erroneous.

Indeed, the prior application makes explicitly clear that the invention embraces any chimeric anti-CD20 antibody having the recited B-cell depleting activity. Also, this application provides explicit support for combination therapies.

In any event, the new claims find express support from the above-identified portions of U.S. Patent 5,736,137, which contains the identical disclosure as U.S. Serial No. 08/149,099. Therefore, the asserted lack of priority from 08/149,099 is not germane to the present claims. If the Examiner maintains this objection, he is respectfully requested to confer with the Special Programs Examiner that is responsible for reviewing enablement/written description issues.

Claims 1 through 4, 6 and 7 were rejected under 35 U.S.C. §102(e) as being anticipated by Anderson et al, USP 5,736,137. At the outset, it is curious that the Examiner states that these claims do not find support in U.S. Patent 5,736,137 (contains identical disclosure as 08/149,099), yet indicates that this same disclosure anticipates these claims. Clarification is requested.

The basis of the rejection is the different inventive entity (inclusion of John Leonard on this application, who is not a named inventor on the previous patent). However, this rejection is respectfully traversed on the basis that the §102(e) date of the subject claims is the same as the cited patent. Therefore, the patent does not qualify as prior art under 35 U.S.C. §102(e).

Claims 1, 2, 4, 5, and 7-10 stand rejected under 35 U.S.C. §102(e) as being anticipated by Kaminski et al, USP 5,595,721.

Also, Claims 1, 4 and 7-10 stand rejected under 35 U.S.C. §102(b) as being anticipated by Press et al, *J. Clin Oncol.*.

Further, Claims 1, 4 and 7-10 stand rejected under 35 U.S.C. §102(b) as being anticipated by Press et al, *Blood*.

These rejections are all respectfully traversed on the basis that none of these references teaches or suggests a non-radiolabeled chimeric anti-CD20 antibody which is capable of effecting substantially total peripheral B-cell depletion within about 24 hours after administration at the recited dosage amount. Instead, the references teach the administration of antibodies wherein the therapeutic efficacy is largely (or totally) based on a therapeutic radiolabel conjugated thereto.

In fact, Kaminski et al merely speculates that the effective function may be "partly responsible for antitumor effects" (*see* Col. 20, lines 28-30). There is absolutely no basis for concluding that B1, by itself, i.e., in the absence of a therapeutic radiolabel, would exhibit the B-cell depleting activity of the claimed anti-CD20 antibody.

Similarly, Press et al fails to teach or suggest a non-radiolabeled chimeric anti-CD20 antibody having the recited B-cell depleting activity. To the contrary, as discussed at page 6 of the application, "extremely high levels (>2 grams) of IF5 (Press antibody)

were reportedly required to deplete circulating tumor cells, and the results were described as being "transient."

Therefore, in contrast to the position taken by the Examiner, the prior art does not teach an anti-CD20 antibody having the depleting activity of the subject chimeric anti-CD20 antibody.

Claims 1, 2, and 4 to 10 further stand rejected under 35 U.S.C. §103 as being unpatentable over Kaminski et al in view of Hellstrom et al.

Kaminski et al has been discussed above. For the reasons set forth therein, it fails to teach or suggest the invention because it does not suggest that a chimeric anti-CD20 antibody could be produced that would possess the depleting activity provided in the claimed methods.

At best, Kaminski et al teaches that the effector function of their murine antibody may be partly attributable to is depleting activity, and even those results are only observed at very high dosages, and further even then seemed to occur only after an RIT dose. (*See* Col. 20, lines 28-51 of Kaminski et al). Therefore, this reference would not teach or suggest the claimed methods.

Hellstrom et al is cited merely based on its disclosure relating to combination therapy. Therefore, the addition of this reference does not cure the deficiency of the rejection.

Withdrawal of the rejection based on Kaminski et al in view of Hellstrom et al is therefore respectfully requested.

Claims 1, 2 and 4-10 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Press et al or Press et al (*Blood*) in view of Hellstrom et al and Robinson et al.

The Press et al references are discussed above. These references do not render obvious the claimed methods as Press et al fail to teach or suggest an anti-CD20 antibody that possesses the B-cell depleting activity required by the claimed methods. Instead, IF5 only exhibits depleting activity at very high dosages. Indeed, this fact is even discussed in the disclosure.

Hellstrom et al is again cited because of its disclosure of the combined usage of an antibody and a chemotherapeutic. The reference, however, also fails to teach or suggest a chimeric anti-CD20 antibody having the depleting activity of the claimed invention.

Robinson et al teaches chimeric anti-CD20 antibodies. However, the reference provides no teaching or suggestion relating to a chimeric anti-CD20 antibody that depletes substantially all peripheral B-cells when administered at a dosage ranging from 0.4 to 20.0 mg/kg, or more specifically the use of such antibody for treating B-cell lymphoma in combination with a chemotherapeutic.

The fact that such a chimeric antibody could be obtained could not have been reasonably predicted based on Robinson et al or the state of the art. This is substantiated by the attached §132 Declaration by Darrell Anderson who discusses the unexpected depleting activity of C2B8 (in relation to other antibodies). (This Declaration was submitted during prosecution of the 5,736,137 patent. It is not necessary to provide a re-executed version.) Moreover, with respect thereto, this argument is consistent with the scope of all the claims. While it is noted that the claims are not limited to C2B8, they require the use of an antibody having the B-cell depleting activity thereof (of C2B8).

The fact that such an antibody could be obtained could not have been predicted from Robinson et al, and in fact was an unexpected result. However, it is still reasonable to conclude, based on this result, that other antibodies having similar depleting activity could be selected for absent undue experimentation.

Withdrawal of the §103 rejection based on Press et al or Press et al in view of Hellstrom et al and Robinson et al is therefore respectfully requested.

Finally, Claims 1-3 and 5-7 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Hellstrom et al in view of Reff et al (*J. Cell Biochem.*), or Anderson et al or Reff et al (*Blood*).

This rejection is respectfully traversed essentially on the basis that the Reff et al (*J. Cell Biochem.*), Anderson et al and Reff et al (*Blood*) references are not prior art to the claimed invention.

The effective filing date of the clams is November 13, 1993, which is the same as the Anderson et al patent, and prior to Reff et al (*Blood*). Moreover, the Reff et al (*J. Cell Biochem.*) article is not prior art as it constitutes the work of the inventors and was published less than one year prior to the effective filing date. This fact is substantiated by a §132 Declaration by the inventors submitted during prosecution of Serial No. 08/149,099, a copy of which is provided herewith.

Therefore, withdrawal of the §103 rejection of Claims 1-3 and 5-7 based on Hellstrom et al in view of Reff et al (*J. Cell Biochem.*), Anderson et al, or Reff et al (*Blood*), is respectfully requested.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited.

Respectfully submitted,

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